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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/825,958	04/16/2004	Robert Chalifour	50291/004002	8214

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EXAMINER	
BALLARD, KIMBERLY A	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 06/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/825,958	CHALIFOUR ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-72* is/are pending in the application.

4a) Of the above claim(s) *62-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/10&5/9/05,5/1/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment to the claims filed 27 April 2006 has been entered in full. Applicant has canceled claims 1-20 and new claims 46-72 have been added. Claims 46-72 are pending.

Election/Restrictions

Applicant's election with traverse of Group I, drawn to methods for preventing and/or treating an amyloid-related disease in a subject, and species election of SEQ ID NO: 13, in the reply filed on 27 April 2006 is acknowledged. The traversal is on the ground(s) that the inventions of new claims 46-72 are related products and processes, wherein the vaccines (claims 62-72) are used in the vaccination methods (claims 46-61), and the vaccination methods employ the vaccines. Applicants submit that in view of the relationship between the claimed methods and vaccines, the claims of Groups I and II should be examined together. This is not found persuasive because, as noted in the Restriction requirement dated 22 March 2006, the vaccine and the method for treating using the vaccine are classified in different subclasses (424/185.1 for the method and 424/130.1 for the vaccine), and thus have acquired a separate status in the art in view of their different classification. And while the inventions of Group II and I, as amended, may now be related as product and process of use, respectively, the inventions can still be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another

materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the method for preventing and/or treating an amyloid-related disease in a subject (Group I) could be practiced instead with a materially different product, for example with an anti-Aβ antibody, and still achieve the desired result of treating a subject by altering levels of amyloid-β in the brain of said subject. Additionally, the vaccine comprising the amyloid-β peptide could be used to recover existing anti-Aβ antibodies from a patient sample, such as in affinity chromatography, and thus could be used in diagnostic testing. Furthermore, the search for the vaccine will not be informative as to the novelty or non-obviousness of the specific method steps recited in Group I. Thus the searches required for the different inventions are not coextensive, so considering them together would be very burdensome to the examiner.

With respect to the species election, Applicants state that SEQ ID NOs: 3,4, 7, 10, 15, 18, 21, 23, 25, 26, 27, 50, 53, 56, 59, and 62 should be examined in addition to SEQ ID NO: 13 because each of these sequences encompasses SEQ ID NO: 13. This argument has been found persuasive and accordingly, the species election requirement is hereby withdrawn.

However, the restriction requirement between Group I and II is still deemed proper and is therefore made **FINAL**.

Claims 62-72 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or

linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 27 April 2006. Claims **46-61** are under examination in the current office action.

Information Disclosure Statement

Signed and initialed copies of the IDS papers submitted 10 March 2005, 9 May 2005, and 1 May 2006 are enclosed in this action.

Priority

For purposes of examination and in determining prior art references, it is noted that the peptides of sequences set forth in SEQ ID NOs: 49-63 were not disclosed in the provisional application 60/168,594 (filed 11/29/1999). SEQ ID NOs: 49-63 were not disclosed until the non-provisional parent application 09/724,842, filed 11/28/2000. Additionally, support for the carrier keyhole limpet hemocyanin (KLH, as in instant claim 53) is only found in the parent application 09/724,842 (see p. 7, line 1) and not in the provisional application. Accordingly, for purposes of prior art, the effective filing date of instant claims **47-50 and 53** is considered to be the filing date of **28 November 2000**, and the effective filing date of claims **46, 51-52, and 54-6**1 is considered to be **29 November 1999**.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 46-51 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 8, and 10 of copending Application No. 10/895,646. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '646 application recites a method for preventing or treating an amyloid-related disease in a subject, comprising administering an antigenic amount of an all-D peptide, wherein said peptide elicits the production of antibodies against said all-D peptide and induces an immune response by said subject, and wherein said peptide is selected from the group consisting of SEQ ID NOS: 1-50 (claim 8 of '646) or the group consisting of SEQ ID NOS: 49-65 (claim 10 of '646). While the amino acid sequences of the two applications do not correspond in terms of their SEQ ID NOS, they do recite the same sequences. For example, SEQ ID NOS: 12, 15, and 55 of the '646 application are identical to SEQ ID NOS: 10, 13, and 53 of the instant application, respectively. The '646 application also recites N-terminal

substituents and C-terminal substituents (claim 2 of '646) which are identical to those of instant claim 51.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 46-51 and 56-61 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/28471 by Findeis et al., published 19 September 1996 (listed on Applicant's IDS filed 3/10/05).

Findeis et al. teaches a method for treating a subject for a disorder associated with amyloidosis, comprising administering to the subject a therapeutically or prophylactically effective amount of a compound of the invention (see p. 7, lines 10-13, and claims 44-47). The method may be used to treat disorders such as Alzheimer's disease (p. 7, lines 30-31), thus anticipating instant claims 58 and 60, as well as hereditary cerebral hemorrhage with amyloidosis of Icelandic type (p. 7, lines 22-23), which is a species anticipating the genus of cerebral amyloid angiopathy recited in instant claim 59. Findeis teaches that the compounds of the invention modulate the aggregation and neurotoxicity of β-amyloid peptides (see Summary of the Invention, p. 3, lines 5-8).

The β-amyloid modulator compounds comprise a modifying group attached directly or indirectly to an Aβ-derived peptidic structure, wherein over 30 peptide sequences are disclosed by Findeis (p. 5, lines 24-37). Two such sequences disclosed by Findeis include SEQ ID NO: 9 (KLVFFA) and SEQ ID NO: 10 (KLVFF). Findeis teaches that such compounds may be modified by substitution of all D-amino acids for all L-amino acids within the compound (p. 17, lines 18-20). Hence, with substitution of all D-amino acids, the sequences comprising or consisting of SEQ ID NOS: 9 and 10 taught by Findeis are identical to the instantly claimed amino acid sequences of SEQ ID NOS: 7 (KLVFFA) and 15 (KLVFF), respectively, recited in instant claims 47-50. Also, both the sequences comprising SEQ ID NOS: 9 and 10 taught by Findeis would encompass instantly claimed SEQ ID NO: 13 (KLVF), thus meeting a limitation of claim 46. Finally, Findeis teaches that the modifying group can be coupled to the amino-

terminus or carboxy-terminus of the Aβ-derived peptidic structure (see p. 25, lines 30-32), and such modifying groups include cyclic, heterocyclic or polycyclic groups, wherein the cyclic group is further taught to have from about 3 to 10 carbon atoms (see p. 26, lines 12-14). If combined with the fact that the natural C-terminus of a peptide is a hydroxyl group (as recited in claim 51(b)), these teachings would thus anticipate the recited limitations within claim 51. And although Findeis does not explicitly state that these compounds elicit an immune response in a subject, the skilled artisan would recognize that the act of administering the Aβ-derived compounds, which are identical to the peptide vaccine instantly claimed, would intrinsically result in the production of anti-amyloidogenic antibodies absent factual evidence to the contrary. Additionally, such anti-amyloidogenic antibodies would inherently alter levels of soluble amyloid-β as well as prevent fibrillogenesis in the brains of those subjects to whom the immunogenic peptides were administered, thus meeting recited limitations of instant claims 56 and 57. Finally, in view of the fact that both the goal of the recited methods (i.e., a method for treating amyloidogenic-associated disease in a subject) and the administered compound are the same for both the instant application and Findeis, the disclosure provided by Findeis would meet the recited limitations within claim 46. Accordingly, Findeis et al. anticipate instant claims 46-51 and 56-61.

Claims 46-61 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 6,743,427 B1 to Schenk, issued 1 June 2004 (listed on Applicant's IDS filed 5/9/05), as evidenced by Kalaria RN (*Ann N Y Acad Sci*, 1999; 893: 113-125).

Schenk teaches β-amyloid peptides, and fragments thereof, effective to evoke an immune response within the host against an amyloid plaque and which administration of the Aβ peptides is effective to reduce amyloid plaque burden in brains exhibiting Alzheimer's type pathology (see columns 9-15 and 33-41). Schenk also teaches a method of preventing or treating a disease associated with amyloid deposits of Aβ in the brain of a patient, comprising administering fragments of Aβ or analogs thereof eliciting an immunogenic response against certain epitopes within Aβ (see column 3, lines 15-22). Schenk teaches that analogs of the Aβ peptides include unnatural amino acids, such as D-amino acids, as well as modifications of N or C terminal amino acids at one, two, or a few positions (see column 11, lines 24-29). Schenk further teaches that the peptide fragment is administered with an adjuvant to enhance the immune response to the Aβ peptide, with such adjuvants including aluminum hydroxide, monophosphoryl lipid A (such as MPL™), QS-21 (Stimulon™) which is a saponin, muramyl peptides, bacterial cell wall components, and cytokines such as IL-12 and granulocyte-macrophage colony stimulating factor (GM-CSF) (see columns 27-28), thus meeting recited limitations of instant claims 54-55. Additionally, Schenk teaches that to help elicit an immune response, the peptide immunogen can be administered fused or otherwise complexed with a carrier protein (see column 15, lines 17-19), such as serum albumins, keyhole limpet hemocyanin (KLH), immunoglobulin molecules, ovalbumin, etc. (see column 20, lines 12-21), thus meeting recited limitations of instant claims 52-53.

One such immunogenic Aβ peptide fragment disclosed by Schenk is SEQ ID NO: 21 (HHQKLVFFAE), which is the same amino acid sequence as SEQ ID NO: 27 of the instant application, and would hence also encompass SEQ ID NO: 13 (KLVF) of the instant application. The Aβ peptides of Schenk would therefore comprise instantly claimed SEQ ID NO: 13 with N-terminal hydrogen and C-terminal hydroxyl (the natural formation of N and C terminal amino acids), thus meeting recited limitations of claims 46-51. Schenk teaches that the immunization of PDAPP mice (a transgenic mouse model of Alzheimer's disease) with Aβ peptide fragments results in significant decreases in both total Aβ levels (a measure of both soluble and insoluble Aβ) and amyloid burden (a measure of aggregated Aβ resulting from fibrillogenesis of Aβ proteins) in the brains of the mice (see columns 44-45 and Figure 12), as well as increases in antibody titers to the immunogenic peptides (see column 46 and Figure 13). Therefore, absent factual evidence to the contrary, the administration of the above immunogenic peptides taught by Schenk to a subject would thus result in the production of anti-amyloidogenic antibodies that would inherently act to both alter levels of soluble Aβ and inhibit fibrillogenesis in the brain of said subject, thus meeting recited limitations of instant claims 56 and 57. Schenk further teaches that these methods can be used to treat Alzheimer's disease (see column 3, lines 17-19). The treatment of Alzheimer's disease would encompass the treatment of cerebral amyloid angiopathy, because vascular lesions such as microvascular degeneration affecting the cerebral endothelium, cerebral amyloid angiopathy and periventricular white matter lesions are evident in virtually all cases of patients with Alzheimer's disease as evidenced by

Kalaria (see, for example, Abstract and Table 1, p. 114). Thus, Schenk anticipates instant claims 46-61.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 52-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/28471 by Findeis et al., published 19 September 1996 (listed on Applicant's IDS), in view of WO 99/27944 by Schenk, published 10 June 1999 (listed on Applicant's IDS).

The teaching of Findeis et al. have been discussed *supra*. Specifically, Findeis teaches the administration of the Aβ peptide sequences KLVFFA and KLVFF (which comprise SEQ ID NO: 13 (KLVF) of the instant application), in a method for treating a subject for a disorder associated with amyloidosis (see p. 7, lines 10-13, and claims 44-47). Findeis teaches that the compounds of the invention modulate the aggregation and neurotoxicity of β-amyloid peptides (see Summary of the Invention, p. 3, lines 5-8). Further, Findeis teaches that such compounds may be modified by substitution of all D-amino acids for all L-amino acids within the compound (p. 17, lines 18-20). The skilled artisan would recognize that the peptide administration would intrinsically induces an antigenic response as evidenced by Schenk above (and below), absent factual evidence to the contrary. However, Findeis does not teach the administration of adjuvants or carrier molecules in conjugation with the administration of anti-amyloidogenic peptides comprising SEQ ID NO: 13.

Schenk teaches β-amyloid peptides, and fragments thereof effective to evoke an immune response within the host against an amyloid plaque, where administration of the peptides is effective to reduce amyloid plaque burden in brains exhibiting Alzheimer's type pathology (see in particular p. 13-15 and 51-53). Schenk teaches that some agents for inducing an immune response contain the appropriate epitope for

inducing an immune response but are too small to be immunogenic. In such cases, Schenk discloses that the peptide immunogens can be linked to a suitable carrier, such as keyhole limpet hemocyanin or GM-CSF, to help elicit an immune response (p. 20, lines 1-10). Additonally, Schenk teaches that the immunogenic peptides can be administered in combination with an adjuvant, such as aluminum hydroxide, monophosphoyrl lipid A, muramyl peptides, bacterial cell wall components, saponin adjuvants, interleukins (IL-1, IL-2, and IL-12), or macrophage colony stimulating factor (M-CSF), among others, to help elicit an immune response (p. 25-27). Schenk also teaches the preparation of such Aβ immunogen vaccines and compares various adjuvants for their ability to potentiate immune responses to Aβ and to induce the immune-mediated clearance of amyloid deposits in the brain (see p. 59-71, particularly Tables 7 and 8 showing the different adjuvants tested and resultant antibody titers). Thus, the artisan recognizes the treatment of amyloidogenic diseases via administration of Aβ peptides comprising the sequence KLVF, not only for the inhibition of β-amyloid aggregation and neurotoxicity, but also for the beneficial property of inducing of an immune response with subsequent immune-mediate clearance of amyloid deposits *in vivo* as recognized by Schenk. It would have been obvious to one of skill in the art at the time the invention was filed to combine the method of modulating the aggregation of amyloidogenic proteins by administering Aβ peptides in conjunction with an adjuvant or carrier protein in order to enhance the immune response to the peptide immunogens. The artisan would be motivated to produce anti-amyloidogenic immunogenic peptides comprising KLVF (SEQ ID NO: 13) in all D-amino acid conformation coupled to a carrier

or administered with an adjuvant, to provide treatment of amyloidogenic diseases as recognized in the art via not only their anti-fibrillogenic properties, but also for their immunogenic property of inducing immune-mediated clearance of amyloid deposits in the brains of subjects administered the peptides. Accordingly, the artisan would be motivated to use carrier proteins or adjuvants in conjunction with the Aβ peptides in order to enhance this immune-mediated amyloid clearance response. Such combination would be met with an expectation of success by the artisan based upon the examples of therapeutic efficacies of various adjuvants used with Aβ peptides comprising SEQ ID NO: 13 to elicit anti-amyloidogenic antibody production and reduction of Aβ brain aggregates as taught by Schenk. Thus, the combined references render the claimed invention obvious to the artisan at the time of filing.

Claims 46-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/27944 by Schenk, published 10 June 1999 (listed on Applicant's IDS), as evidenced by Alberts et al. (Molecular Biology of the Cell, 2nd Edition, Garland Publishing Inc., 1989, p. 54, listed on Applicant's IDS) and Kalaria RN (*Ann N Y Acad Sci*, 1999; 893: 113-125), and in view of Tjernberg et al. (*J Biol Chem*, 1996; 271(15): 8545-8548, listed on Applicant's IDS), WO 96/28471 by Findeis et al., published 19 September 1996 (as listed on Applicant's IDS), Van Regenmortel et al. (*Curr Opin Biotechnology*, 1998; 9: 377-382, as on IDS), US 4,116,768 to Isowa et al., issued 26 September 1978 (listed on Applicant's IDS), and US 6,436,903 B1 to Clayberger et al., issued 20 August 2002, filed 22 May 1996.

Schenk teaches β-amyloid peptides, and fragments thereof effective to evoke an immune response within the host against an amyloid plaque, where administration of the peptides is effective to reduce amyloid plaque burden in brains exhibiting Alzheimer's type pathology (see in particular p. 13-15 and 51-53). Schenk also teaches a method of preventing or treating a disease characterized by amyloid deposits in a patient comprising administering an agent effective to induce an immune response against a peptide component of an amyloid deposit in the patient, wherein the amyloid deposit comprises aggregated Aβ peptide, and wherein the immunizing peptide or agent is Aβ peptide (see in particular clams 8-23). Schenk teaches that the immunogenic peptides can be linked to a suitable carrier, such as keyhole limpet hemocyanin or GM-CSF, to help elicit an immune response (p. 20, lines 1-10), or administered in combination with an adjuvant, such as aluminum hydroxide, monophosphoyrl lipid A, muramyl peptides, bacterial cell wall components, saponin adjuvants, interleukins (IL-1, IL-2, and IL-12), and macrophage colony stimulating factor (p. 25-27). Schenk additionally teaches that the peptide immunogens may include unnatural amino acids or modifications of N or C terminal amino acids (p. 15). The β-amyloid peptides of Schenk, particularly Aβ13-28 (which is the same as instantly claimed SEQ ID NO: 4) and full length Aβ aggregates AN1792 and AN1528, comprise several of the instantly claimed peptides, such as SEQ ID NOS: 3, 4, 7, 10, 13, 15, 18, 21, 23, 25, 26, and 27 with N' terminal hydrogen (the natural formation of N' terminal amino acids, see in particular, Alberts, p. 54 exhibiting N' terminal hydrogen bonds). Schenk teaches that immunization of PDAPP mice (a transgenic mouse model of Alzheimer's disease) with

Aβ peptide fragments results in significant decreases in both total Aβ levels (a measure of both soluble and insoluble Aβ) and amyloid burden (a measure of aggregated Aβ resulting from fibrillogenesis of Aβ proteins) in the brains of the mice (see p. 51-54), as well as increases in antibody titers to the immunogenic peptides (see p. 54-55). Finally, Schenk discloses that these methods can be used to treat Alzheimer's disease and other amyloidogenic diseases (see Background and Summary, p. 1-3). The treatment of Alzheimer's disease would encompass the treatment of cerebral amyloid angiopathy, because vascular lesions such as microvascular degeneration affecting the cerebral endothelium, cerebral amyloid angiopathy and periventricular white matter lesions are evident in virtually all cases of patients with Alzheimer's disease as evidenced by Kalaria (see, for example, Abstract and Table 1, p. 114).

However, Schenk does not teach that the peptides comprising the above sequences consist entirely of D-amino acids, or peptides comprising specific N or C terminal substituents (as recited in claim 51), or amino acid substitutions such as thienylalanine, cyclohexylalanine, or phenylglycine (such as are found in instantly claimed SEQ ID NOS: 56, 59, and 62).

Tjernberg et al. teach that peptides incorporating a short Aβ fragment (KLVFF; Aβ16-20) can bind full-length Aβ and prevent its assembly into amyloid fibrils *in vitro* (see Abstract and p. 8547). Tjernberg also proposes that such peptides may serve as lead compounds for the development of peptide and non-peptide agents aimed at inhibiting Aβ amyloidogenesis *in vivo*, such as for the treatment of Alzheimer's disease (see Abstract and p. 8548).

The teachings of Findeis have been discussed *supra*. Specifically, Findeis teaches the administration of the Aβ peptide sequences KLVFFA and KLVFF (which are identical to instantly claimed SEQ ID NOS: 7 and 15, and which would also comprise SEQ ID NO: 13 (KLVF) of the instant application), in a method for treating a subject for a disorder associated with amyloidosis (see p. 7, lines 10-13, and claims 44-47), such as Alzheimer's disease (p. 7, lines 30-31), as well as hereditary cerebral hemorrhage with amyloidosis of Icelandic type (p. 7, lines 22-23), a species anticipating the genus of cerebral amyloid angiopathy recited in instant claim 59. Findeis teaches that the compounds of the invention modulate the aggregation and neurotoxicity of β-amyloid peptides (see Summary of the Invention, p. 3, lines 5-8). Findeis teaches that such compounds may be modified by substitution of all D-amino acids for all L-amino acids within the compound (p. 17, lines 18-20). Finally, Findeis teaches that modifying groups can be coupled to the amino-terminus or carboxy-terminus of the Aβ-derived peptidic structure (see p. 25, lines 30-32), and such modifying groups include cyclic, heterocyclic or polycyclic groups, wherein the cyclic group is further taught to have from about 3 to 10 carbon atoms (see p. 26, lines 12-14). The peptide administration intrinsically induces an antigenic response as evidenced by Schenk above, absent factual evidence to the contrary.

Van Regenmortel et al. further recognize the use of peptides assembled partly or totally from D-amino acids as being much more stable to proteolysis than natural L-peptides and having considerable potential as synthetic vaccines and as immunomodulators in T-cell responses (see Abstract, p. 377). Van Rengenmortel

further notes that lower doses of D-polymers are needed than the corresponding L-polymers to induce an immunogenic response (see p. 377, 2nd column).

Isowa et al. (US 4,116,768) teach the recognition of the art of the preparation of N- and C-terminal protective groups for stabilization of peptide compounds *in vivo* (see in particular columns 3-4). For example, Isowa teaches that C-terminal protective groups include alkoxy groups as well as substituted or unsubstituted amino groups. Isowa also teaches that suitable protective groups for the free N-terminal include alkoxycarbonyl groups, benzyoxycarbonyl groups, and the like, which includes acyclic and cyclic akyl groups.

Clayberger et al. (US 6,436,903) teach the production of immunomodulating peptide compounds comprising D-amino acids, including N-terminal acylated and C-terminal amidated forms of up to 30 amino acids (see Abstract). Clayberger teaches that the N-terminus of the compound may be in the free amino form or may be acylated by a group of the formula RCO-, wherein R represents a hydrocarbyl group of 1-6 carbon atoms, and wherein the hydrocarbl group is saturated or unsaturated and is acyclic or cyclic (see column 5, lines 29-38). Clayberger also teaches that the C-terminus of the compounds may be in the underivatized carboxyl group, or may be esterified or amidated. Clayberger further teach that certain commonly encountered amino acids, which are not encoded by the genetic code, may be used in conservative substitutions, in which an amino acid, which is of the same general group as that for which substitution is made, replaces the referent amino acids (see columns 3-4). For example, substitution of phenylalanine, a hydrophobic residue, could be made with

phenylglycine (Phg), cyclohexylalanine (Cha), or P 2-thienylalanine (Thi), which are all hydrophobic residues (see in particular column 4, lines 49-65).

Thus, the artisan recognizes the treatment of amyloidogenic diseases, such as Alzheimer's disease and resultant cerebral amyloid angiopathy, via administration of immunogenic doses of β-amyloid peptides *in vivo*, and further recognizes the additionally advantageous properties of peptides comprising the sequence KLVFF, not only for the induction of an immune response as recognized by Schenk, but also for the additional properties of inhibiting amyloid fibril formation *in vitro* and its suggested use *in vivo* for inhibiting amyloid plaque formation. Moreover, the artisan recognizes amino terminal group hydrogen on naturally occurring peptides as well as N-terminal substituent protective groups, and C-terminal carboxyl groups on naturally occurring peptides as well as C-terminal substituent protective groups and substituted and unsubstituted amino groups to stabilize such pharmaceuticals *in vivo*. The artisan also recognizes the benefits of all D-amino acid peptide as being resistant to catabolism and the importance of conservative substitutions of amino acids within the peptide compounds, as collectively taught by Van Rengenmortel, Findeis, and Clayberger. Further, the artisan would recognize the advantage of administering such peptides either coupled to a carrier or comprising an adjuvant to enhance the immunogenic response, particularly to small peptide molecules, as disclosed by Schenk. Thus, the artisan understanding these principles would be motivated to produce anti-amyloidogenic immunogenic peptides comprising KLVF (SEQ ID NO: 13) in all D-amino acid conformation, with or without N- or C-terminal protective groups, with or without

conservative amino acid substitutions (as in instantly claimed SEQ ID NOS: 56, 59, and 62) and coupled to a carrier or administered with an adjuvant, to provide treatment of Alzheimer's disease (and cerebral amyloid angiopathy) as recognized in the art via both its immunogenic and anti-fibrillogenic properties. One of skill in the art would be specifically motivated to produce the peptide in D-amino acid conformation and with N- or C-terminal substituent protective groups based upon the art recognized teachings of greater stability and resistance to proteolysis of these molecules *in vivo* while retaining both anti-fibrillogenic and immunostimulatory properties. Such modification would be met with an expectation of success by the artisan based upon the conservation of immunogenic and anti-fibrillogenic properties within the host while providing the advantages of a compound with increased half-life with resistance to catabolism, such that lower pharmacologic doses need to be administered. Thus, the cumulative reference teachings render the claimed invention obvious to the artisan at the time of filing.

Conclusion

All claims are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Art Unit 1649
June 8, 2006

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